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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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RE: Docket No. 2003D-0412: International Conference on Harmonization; Draft Guidance on E2D Postapproval Safety Data Management: Definitions and Standards for Expedited Reporting

Merck & Co., Inc. is a leading worldwide, human health product company. Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck supports regulatory oversight of pharmaceutical products throughout their life cycle and welcomes regulatory revisions that are based on sound scientific principles and good judgment. Merck has participated with health authorities from around the globe in the harmonization of regulatory standards under the auspices of the International Conference on Harmonization (ICH). The objectives of ICH have been to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical products caused by incompatible regulatory schemes. We continue to monitor the equitable and consistent application of these harmonized standards to product development in order to ensure that *new* or *improved* therapies reach patients as swiftly as possible.

As a leading pharmaceutical company, Merck has extensive experience in thoroughly evaluating our products from discovery to approval and throughout their marketing life to assure that they continue to provide health benefits with minimum risk. All of our products undergo continuous safety assessment. Safety reporting to regulatory agencies is an integral part of the process. Because of our experience, both with international harmonization efforts and product safety reporting, we are well qualified to comment on the above cited ICH Draft Guidance on postapproval safety data management.

General Comment

Merck supports and encourages efforts to harmonize technical regulatory requirements for the development and marketing of pharmaceutical products around the world. We have reviewed the ICH Harmonised Tripartite Guideline draft, "Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting," (ver. 3.8) that

was recommended for adoption at Step 2 of the ICH process on July 18, 2003 by the ICH Steering Committee. In general, we agree with the provisions of this draft guideline.

Specific Comments

1. Section 2.1.2 (lines 108-109), which defines the term "Adverse Drug Reaction" (ADR) and Section 3.1.1 (line 282), which describes standards for expedited reporting of single cases of serious *ADRs,* include appropriate statements regarding causality using the terms "at least a possibility" and "possible causal relationship". The general reference to ICH E2A in Section 2.1.2, however, creates ambiguity in ICH E2D because the definition of ADR in ICH E2A includes a statement implying that the term "reasonable possibility" means "the relationship cannot be ruled out." Language in subsequent sections of ICH E2A clarifies its treatment of "causality," and, therefore, we believe that specific reference to these sections would be more appropriate. This is especially important since the ICH E2D discussion of the definition of ADR notes that "the phrase 'responses to a medicinal product' means that a causal relationship...is at least a possibility." In particular, we recommend reference to ICH E2A Section III.A. in which it states, "For purposes of reporting, adverse event reports associated with marketed drugs (spontaneous reports) usually imply causality" and "the expression 'reasonable causal relationship' is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.' Reference to "the relationship cannot be ruled out" should be removed.

2. Section 2.3 (lines 144, 146-147, 158, and 165) refers to "official product information" in its discussion of "Unexpected Adverse Drug Reactions." Because products may have national, European, and global (core) product information, the meaning of the guideline would be improved if the term "official product information" was more specifically defined. Ideally, specifying that "official product information" refers to the Company Core Safety Information (CCSI), as defined in ICH E2C, would serve this function.

3. Section 2.5.3. refers to "Licensor-Licensee Interaction." On lines 265-266, the draft guideline states, "Any subsequent follow-up information sent to the regulators should be submitted by the same MAH that reported the case originally." In the event of transfer of ownership of applications (including transfers related to mergers, and acquisitions), however, we recommend allowance be made for subsequent follow-up to be reported by the successor MAH unless otherwise stipulated in documents related to the transfer.

4. Section 2.5.4 refers to "Regulatory Authority Sources." Although lines 269-270 state "Individual serious unexpected adverse drug reaction reports originating from foreign regulatory authorities are always subject to expedited reporting," we recommend clarification to indicate specifically that reports from regulatory authorities that are subject to expedited reporting be limited to those received from health care professionals. In the absence of this clarification, all serious, unexpected reports from

consumers included on listings received from FDA through Freedom of Information would become expedited reports for the EU.

5. Section 4.2 (lines 371-372) states that "Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available...." We recommend that routine submission of these documents should not be required since the ICH E2B format provides industry with the means to record the existence of such documents and allows agencies to request hard copies. Routine submission will only create additional administrative burden on both agencies and sponsors without added benefit since the key information is already included in the narrative and the availability of the documents is stated with supply upon request. In addition, this requirement may have implications on patient confidentiality issues for both U.S. and foreign data.

6. Section 4.4 (lines 427-428) refers to collaboration between MAHs in the event that more than one MAH's drug is suspected as a causal agent. Apart from where there are pre-existing agreements with "business partners," the statement regarding collaboration to obtain follow up information is not particularly practical or realistic given the inherent constraints related to confidentiality, data privacy, and tight reporting timeframes. Therefore, we recommend that this statement be omitted.

7. The attachment, "Recommended Key Data Elements for Inclusion in Expedited Reports of Serious Adverse Drug Reactions," is not totally consistent with ICH E2B. Given that section 4.5 refers to the implementation of ICH E2B/M2 standards, we recommend that E2B/M2 be referenced instead, and that the field examples in the attachment represent examples of data that one needs to consider.

Conclusion

In conclusion, Merck fully supports and encourages international harmonization efforts and, in general, we agree with the recommendations in the ICH E2D draft guideline. We request consideration of the points of clarification we have recommended in our specific comments which, we believe, will further the ongoing efforts toward international harmonization.

We appreciate the opportunity to comment on this draft ICH guideline.

Sincerely,

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